

For the use of only a registered medical practitioner or Hospital / institutional staff.

PREScribing INFORMATION

Brivaracetam Oral Solution 10 mg/mL

BrivaneX™

विवारेचेटम

1. GENERIC NAME

Brivaracetam 10mg/mL Oral solution

2. COMPOSITION

Each mL contains

Brivaracetam—10 mg

3. DOSAGE FORM AND STRENGTH

Brivaracetam is available as 10 mg/mL oral solution

4. CLINICAL PARTICULARS

4.1. Indications

Brivaracetam oral solution is indicated as an adjunctive therapy in the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.

4.2. Posology and Method of Administration

Dosage Information

The physician should prescribe the most appropriate formulation and strength according to weight and dose.

Monotherapy or Adjunctive Therapy

When initiating treatment, gradual dose escalation is not required. The recommended starting dosage is 50 mg twice daily (100 mg per day). Based on individual patient tolerability and therapeutic response, the dosage may be adjusted down to 25 mg twice daily (50 mg per day) or up to 100 mg twice daily (200 mg per day).

Administration Instructions for Brivaracetam Oral Solution

A calibrated measuring device is recommended to measure and deliver the prescribed dose accurately. A household teaspoon or tablespoon is not an adequate measuring device.

Discontinuation of Brivaracetam

Avoid abrupt withdrawal from Brivaracetam in order to minimize the risk of increased seizure frequency and status epilepticus.

Patients with Hepatic Impairment

For all stages of hepatic impairment, the recommended starting dosage for adults and pediatric patients weighing 50 kg or more is 25 mg twice daily (50 mg per day), and the recommended maximum dosage is 75 mg twice daily (150 mg per day). The recommended starting dosage for pediatric patients with hepatic impairment weighing 11 kg to less than 50 kg is 0.5 mg/kg twice daily (1 mg/kg per day). The maximum dosage for pediatric patients with hepatic impairment weighing 20 kg to less than 50 kg is 1.5 mg/kg twice daily (3 mg/kg per day). The maximum dosage for pediatric patients with hepatic impairment weighing 11 kg to less than 20 kg is 2 mg/kg twice daily (4 mg/kg per day).

Co-administration with Rifampin

Increase the Brivaracetam dosage in patients on concomitant rifampin by up to 100% (i.e., double the dosage).

4.3. Contraindications

Hypersensitivity to Brivaracetam or any of the inactive ingredients in Brivaracetam (bronchospasm and angioedema have occurred).

4.4. Special Warnings and Precautions for Use

Suicidal Behaviour and Ideation

Antiepileptic drugs (AEDs), including Brivaracetam, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed.

Anyone considering prescribing Brivaracetam or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Neurological Adverse Reactions

Brivaracetam causes somnolence, fatigue, dizziness, and disturbance in coordination. Patients should be monitored for these signs and symptoms and advised not to drive or operate machinery until they have gained sufficient experience on Brivaracetam to gauge whether it adversely affects their ability to drive or operate machinery.

Somnolence and Fatigue

Brivaracetam causes dose-dependent increases in somnolence and fatigue-related adverse reactions (fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy. The risk is greatest early in treatment but can occur at any time).

Dizziness and Disturbance in Gait and Coordination

Brivaracetam causes adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, vertigo, balance disorder, ataxia, nystagmus, gait disturbance, and abnormal coordination). The risk is greatest early in treatment but can occur at any time.

Psychiatric Adverse Reactions

Brivaracetam causes psychiatric adverse reactions. Psychiatric events included both non-psychotic symptoms (irritability, anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mood, tearfulness, apathy, altered mood, mood swings, affect lability, psychomotor hyperactivity, abnormal behavior, and adjustment disorder) and psychotic symptoms (psychotic disorder along with hallucination, paranoia, acute psychosis, and psychotic behavior).

Hypersensitivity: Bronchospasm and Angioedema

Brivaracetam can cause hypersensitivity reactions. Bronchospasm and angioedema have been reported in patients taking Brivaracetam. If a patient develops hypersensitivity reactions after treatment with Brivaracetam, the drug should be discontinued. Brivaracetam is contraindicated in patients with a prior hypersensitivity reaction to Brivaracetam or any of the inactive ingredients.

Withdrawal of Antiepileptic Drugs

As with most antiepileptic drugs, Brivaracetam should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

4.5. Drug Interactions

Rifampin

Co-administration with rifampin decreases Brivaracetam plasma concentrations likely because of CYP2C19 induction. Prescribers should increase the Brivaracetam dose by up to 100% (i.e., double the dosage) in patients while receiving concomitant treatment with rifampin.

Carbamazepine

Co-administration with carbamazepine may increase exposure to carbamazepine-epoxide, the active metabolite of carbamazepine. Though available data did not reveal any safety concerns, if tolerability issues arise when co-administered, carbamazepine dose reduction should be considered.

Phenytoin

Because Brivaracetam can increase plasma concentrations of phenytoin, phenytoin levels should be monitored in patients when concomitant Brivaracetam is added to or discontinued from ongoing phenytoin therapy.

Levetiracetam

Brivaracetam provided no added therapeutic benefit to levetiracetam when the two drugs were co-administered.

4.6. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy Category C

There are no adequate data on the developmental risks associated with use of Brivaracetam in pregnant women. In animal studies, brivaracetam produced evidence of developmental toxicity (increased embryofetal mortality and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, and long-term neurobehavioral changes in rat offspring) at maternal plasma exposures greater than clinical exposures. Oral administration of brivaracetam (0, 150, 300, or 600mg/kg/day) to pregnant rats during the period of organogenesis did not produce any significant maternal or embryofetal toxicity.

Oral administration of brivaracetam (0, 30, 60, 120, or 240 mg/kg/day) to pregnant rabbits during the period of organogenesis resulted in embryofetal mortality and decreased fetal body weights at the highest dose tested, which was also maternally toxic. When brivaracetam (0, 150, 300, or 600 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation (female), and long-term neurobehavioral changes were observed in the offspring at the highest dose.

Brivaracetam was shown to readily cross the placenta in pregnant rats after a single oral (5 mg/kg) dose of ¹⁴C-brivaracetam. [Reference: BRIVIACT US FDA Label. Dated: May 2018].

Lactation

No data are available regarding the presence of Brivaracetam in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Studies in lactating rats have shown excretion of Brivaracetam or metabolites in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Brivaracetam and any potential adverse effects on the breast fed infant from Brivaracetam or from the underlying maternal condition.

Following a single oral (5 mg/kg) dose of ¹⁴C-brivaracetam to lactating rats, radioactivity was secreted in milk and rapidly reached levels similar to those in plasma [Reference: BRIVIACT US FDA Label. Dated: May 2018].

Pediatric Use

Safety and effectiveness of Brivaracetam in adolescents 16 years of age have been established.

Safety and effectiveness of Brivaracetam in patients less than 16 years of age have not been established.

Geriatric Use

In general, dose selection for an elderly patient should be judicious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

Dose adjustments are not required for patients with impaired renal function. There are no data in patients with end-stage renal disease undergoing dialysis, and use of Brivaracetam is not recommended in this patient population.

Hepatic Impairment

Because of increases in Brivaracetam exposure, dosage adjustment is recommended for all stages of hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Abuse

Brivaracetam at the recommended single dose (50 mg) caused fewer sedative and euphoric effects than alprazolam; however, Brivaracetam at supratherapeutic single doses (200mg and 1000 mg) was similar to alprazolam on other measures of abuse.

Dependence

There was no evidence of physical dependence potential or a withdrawal syndrome with Brivaracetam.

4.7. Effects on Ability to Drive and Use Machines

Brivaracetam has minor or moderate influence on the ability to drive and use machines.

Due to possible differences in individual sensitivity some patients might experience somnolence, dizziness, and other central nervous system (CNS) related symptoms. Patients should be advised not to drive a car or to operate other potentially hazardous machines until they are familiar with the effects of Brivaracetam on their ability to perform such activities.

4.8. Undesirable Effects

Adverse reactions are listed by System Organ Class (SOC) and within each frequency grouping [Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$)] the adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions from clinical trials
Infections and infestations	Common	Influenza
Blood and lymphatic system disorders	Uncommon	Neutropenia
Metabolism and nutrition disorders	Common	Decreased appetite
Immune system disorders	Uncommon	Type I hypersensitivity
Psychiatric disorders	Common	Depression, anxiety, insomnia, irritability
	Uncommon	Suicidal ideation, psychotic disorder, aggression, agitation
Nervous system disorders	Very common	Dizziness, somnolence
	Common	Convulsion, vertigo
Respiratory, thoracic and mediastinal disorders	Common	Upper respiratory tract infections, cough
Gastrointestinal disorders	Common	Nausea, vomiting, constipation
General disorders and administration site conditions	Common	Fatigue

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

There is limited clinical experience with Brivaracetam overdose in humans. Somnolence and dizziness were reported in a patient taking a single dose of 1400 mg (14 times the highest recommended single dose) of Brivaracetam. The following adverse reactions were reported with Brivaracetam overdose: vertigo, balance disorder, fatigue, nausea, diplopia, anxiety, and bradycardia. In general, the adverse reactions associated with Brivaracetam overdose were consistent with the known adverse reactions.

There is no specific antidote for overdose with Brivaracetam. In the event of overdose, standard medical practice for the management of any overdose should be used. An adequate airway, oxygenation, and ventilation should be ensured; monitoring of cardiac rate and rhythm and vital signs is recommended. A certified poison control center should be contacted for updated information on the management of overdose with Brivaracetam. There are no data on the removal of Brivaracetam using hemodialysis, but because less than 10% of Brivaracetam is excreted in urine, hemodialysis is not expected to enhance Brivaracetam clearance.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

The precise mechanism by which Brivaracetam exerts its anticonvulsant activity is not known. Brivaracetam displays a high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, which may contribute to the anticonvulsant effect.

5.2 Pharmacodynamic Properties

Interaction with Alcohol

In a pharmacokinetic and pharmacodynamic interaction study in healthy subjects, co-administration of Brivaracetam (single dose 200 mg [2 times

greater than the highest recommended single dose]) and ethanol (continuous intravenous infusion to achieve a blood alcohol concentration of 60 mg/100 mL during 5 hours) increased the effects of alcohol on psychomotor function, attention, and memory. Co-administration of Brivaracetam and ethanol caused a larger decrease from baseline in saccadic peak velocity, smooth pursuit, adaptive tracking performance, and Visual Analog Scale (VAS) alertness, and a larger increase from baseline in body sway and in saccadic reaction time compared with Brivaracetam alone or ethanol alone. The immediate word recall scores were generally lower for Brivaracetam when co-administered with ethanol.

Cardiac Electrophysiology

At a dose 4 times the maximum recommended dose, Brivaracetam did not prolong the QT interval to a clinically relevant extent. [Reference: BRIVIACT US FDA Label. Dated: May 2018].

5.3 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of Brivaracetam is similar when used as monotherapy or as adjunctive therapy for the treatment of partial onset seizures. Brivaracetam tablets, oral solution, and injection can be used interchangeably. Brivaracetam film-coated tablets, oral solution and solution for intravenous injection show the same AUC, while the maximum plasma concentration is slightly higher after intravenous administration. Brivaracetam exhibits linear and time-independent pharmacokinetics with low intra- and inter-subject variability, and features complete absorption, very low protein binding, renal excretion following extensive biotransformation, and pharmacologically inactive metabolites.

Absorption

Brivaracetam is rapidly and completely absorbed after oral administration and the absolute bioavailability is approximately 100 %. The median t_{max} for tablets taken without food is 1 hour (t_{max} range is 0.25 to 3 h).

Coadministration with a high-fat meal slowed down the absorption rate (median t_{max} 3 h) and decreased the maximum plasma concentration (37 % lower) of Brivaracetam, while the extent of absorption remained unchanged.

Distribution

Brivaracetam is weakly bound to plasma proteins ($\approx 20\%$). The volume of distribution is 0.5 L/kg, a value close to that of the total body water. Brivaracetam is rapidly and evenly distributed in most tissues.

Elimination

Brivaracetam is primarily metabolized by hydrolysis of the amide moiety to form the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite. The hydrolysis reaction is mediated by hepatic and extra-hepatic amidase. The hydroxylation pathway is mediated primarily by CYP2C19. In